High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women

Beulens, Joline W. J.; de Bruijne, Leonie M.; Stolk, Ronald P.; Peeters, Petra H. M.; Bots, Michiel L.; Grobbee, Diederick E.; van der Schouw, Yvonne T.

Published in:
Journal of the American College of Cardiology

DOI:
10.1016/j.jacc.2007.02.068

Publication date:
2007

Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 50, No. 1, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.02.068

High Dietary Glycemic Load and Glycemic Index Increase Risk of Cardiovascular Disease Among Middle-Aged Women

A Population-Based Follow-Up Study

Joline W. J. Beulens, PHD, Leonie M. de Bruijne, MSC, Ronald P. Stolk, MD, PHD, Petra H. M. Peeters, MD, PHD, Michiel L. Bots, MD, PHD, Diederick E. Grobbee, MD, PHD, Yvonne T. van der Schouw, PHD

Utrecht, the Netherlands

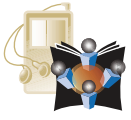
Objectives The goal of this work was to assess whether high dietary glycemic load and glycemic index are associated with an increased risk of cardiovascular disease (CVD).

Background The associations of dietary glycemic index and glycemic load with risk of CVD are not well established, particularly in populations consuming modest glycemic load diets. Moreover, risk may differ between lean and overweight subjects.

Methods Associations of glycemic index and glycemic load with incident CVD were examined in a prospective cohort of 15,714 Dutch women age 49 to 70 years without diabetes or CVD. Dietary glycemic index and glycemic load were calculated using the glycemic index, carbohydrate content, and frequency of intake of individual foods.

Results During 9 ± 2 years of follow-up, 556 cases of coronary heart disease (CHD) and 243 cases of cerebrovascular accident (CVA) occurred. Dietary glycemic load (mean = 100; SD = 17) was associated with increased risk of CVD, adjusted for CVD risk factors and dietary variables, with a hazard ratio (HR) for the highest against lowest quartile of 1.47 (95% confidence interval [CI] 1.04 to 2.09; $p_{trend} = 0.03$). Similar results were observed for dietary glycemic index with a corresponding HR of 1.33 (95% CI 1.07 to 1.67; $p_{trend} = 0.02$). Glycemic load tended to be associated with both CHD (HR 1.44; 95% CI 0.95 to 2.19; $p_{trend} = 0.14$) and CVA (HR 1.55; 95% CI 0.81 to 2.97; $p_{trend} = 0.10$), but glycemic index only with CHD (HR 1.44; 95% CI 1.10 to 1.89; $p_{trend} = 0.01$). Among overweight women (body mass index >25 kg/m^2), glycemic load was associated with CVD (1.78; 95% CI 1.11 to 2.85; $p_{trend} = 0.04$), but not among normal weight women ($p_{interaction} = 0.19$). Body mass index did not modify the association of glycemic index with CVD.

Conclusions Among women consuming modest glycemic load diets, high dietary glycemic load and glycemic index increase the risk of CVD, particularly for overweight women. (J Am Coll Cardiol 2007;50:14–21) © 2007 by the American College of Cardiology Foundation



Journal Club Selection
www.jacccjc.org

The finding that high saturated fat diets increase the risk of cardiovascular disease (CVD) led to recommendations to reduce total and saturated fat intake and a subsequent increase of carbohydrate intake (1). However, such low-fat, high-carbohydrate diets adversely affect lipid and glucose metabolism, leading to insulin resistance (2).

See page 22

Until recently, carbohydrates were classified either as simple or complex believing that saccharide chain length determines the rates of digestion and absorption (3). However, dietary carbohydrates with different structures, particle sizes, and fiber contents are digested and absorbed at different rates and give rise to different blood glucose and insulin responses (4). Rapidly absorbed carbohydrates that induce high postprandial glucose and insulin responses have a high glycemic index. Glycemic load represents both quantity and quality of carbohydrates and is calculated as the product of glycemic index of a specific food and its carbohydrate content (5). Therefore, a food can have a high glycemic index, but low glycemic load, depending on its carbohydrate content.

From the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands.

Manuscript received November 10, 2006; revised manuscript received February 5, 2007, accepted February 12, 2007.

Abdominal obesity, insulin resistance, and dyslipidemia are key components of the metabolic syndrome and are all independently associated with CVD (6). Each 20-mg/dl (0.5 mmol/l) increase of total cholesterol is associated with a 12% increase of coronary heart disease (CHD) mortality (7). Overweight increases the risk of CHD 2-fold, but accounts for almost one-half of the cases because of its high prevalence (8). Diabetes is associated with 3-fold higher risk of CHD, but this risk increases with increasing duration of diabetes (9).

Because dietary glycemic load is a determinant of hyperlipidemia (1), diabetes (5,10), and potentially overweight (11), glycemic load may also be a risk factor for CVD. However, few studies so far explored this association, and data are particularly scarce for populations consuming modest glycemic load diets. A first study by Liu et al. (12) reported a positive association of glycemic load with CHD that was most evident among overweight women. Recently these results have been confirmed in an extended analysis from this study (13). A small study by van Dam et al. (14), however, did not find such relation. A more recent study by Oh et al. (15) only observed a positive association of glycemic load with stroke among overweight women.

We, therefore, investigated the association between dietary glycemic load and glycemic index with CVD in a cohort of 15,714 Dutch women, consuming modest glycemic load diets, and specifically whether this association was modified by body mass index (BMI).

Abbreviations and Acronyms

BMI = body mass index
CHD = coronary heart disease
CI = confidence interval
CRP = C-reactive protein
CVA = cerebrovascular accidents
CVD = cardiovascular disease
FFQ = food frequency questionnaire
HDL = high-density lipoprotein
HR = hazard ratio
HRT = hormone replacement therapy
ICD-9-CM = International Classification of Diseases-Ninth Revision-Clinical Modification
LDL = low-density lipoprotein
OC = oral contraceptives

Methods

Population. Between 1993 and 1997, we recruited 17,357 women age 49 to 70 among breast cancer screening participants in the Prospect-EPIC cohort, 1 of 2 Dutch contributions to the EPIC (European Prospective Investigation into Cancer and Nutrition) study (16). The design, sampling strategies, and examination techniques of the cohort have been described previously (17). All women signed informed consent before study inclusion. The study complies with the Declaration of Helsinki and was approved by the Institutional Review Board of the University Medical Center Utrecht. Of the 17,357 women, we excluded 355 women who did not consent to linkage with vital status registries, 117 women because of missing questionnaires, and 92 women who reported an energy intake of <500 kcal/day or >6,000 kcal/day. Furthermore, 628 women reported a history of CHD (International Classification of Diseases-Ninth Revision-Clinical Modification [ICD-9-CM] 410 to 414, 427.5) or cerebrovascular disease (ICD-9-CM 430 to 438) before the baseline measurements and were, therefore, excluded from the analysis. Finally, 451 women with established diabetes were also excluded, leaving 15,714 women available for analysis. From the original cohort of 17,357 women, a 10% random sample was drawn and the same exclusion criteria were applied, leaving 1,417 women. Blood samples from this random sample were used for determination of biomarkers.

Baseline measurements. At baseline, a general questionnaire containing questions on demographic characteristics, the presence of chronic diseases and their risk factors was administered. Systolic and diastolic blood pressures were measured in duplicate at the left arm with the subjects in sitting position after 10 min of rest with an automated and calibrated oscillomat (Bosch & Son, Jungingen, Germany). Subsequently, the mean systolic and diastolic blood pressure was calculated. Body height was measured to the nearest 0.5 cm with a wall-mounted stadiometer (Lameris, Utrecht, the Netherlands). Body weight was measured in light indoor clothing without shoes to the nearest 0.5 kg with a floor scale (Seca, Atlanta, Georgia). Body mass index was calculated as weight divided by height squared (kg/m^2). Smokers were categorized as never, past, current 1 to 10 cigarettes, current 11 to 20 cigarettes, or current >20 cigarettes. Women were assumed to be postmenopausal when they reported not having menstrual periods for at least a year. Oral contraceptive (OC) use and postmenopausal hormone replacement therapy (HRT) use was defined as ever versus never. Hypertension and hypercholesterolemia were defined as present when women reported that a physician had diagnosed these disorders. Physical activity was assessed by a questionnaire including items on household, sports, and other leisure time activities, validated in healthy people, age 63 to 80 years (18). Spearman correlations with scores from repeated 24-h activity recalls and pedometer measurements were 0.78 and 0.73, respectively. We could not calculate a total physical activity score for 1,220 women with incomplete questionnaires. These missing total scores were imputed by means of linear regression modeling, which predicts the value of a missing variable by using all available data from individual questions of the questionnaire, and reduces bias, since missing data may not occur at random (19). At baseline, all women donated a nonfasting blood sample, and biomarkers were determined for the random sample. Total cholesterol and glucose were determined using an automated enzymatic procedure on a Vitros 250 (Johnson & Johnson, Rochester, New York), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels using a colorimetric assay on a Hitachi 904 (Johnson & Johnson), and plasma high-

sensitive C-reactive protein (CRP) using the Behring BNII nephelometric method (Dade Behring, Deerfield, Illinois).

Food frequency questionnaire (FFQ). Food intake was assessed using a validated FFQ including questions on the usual frequency of consumption of 77 main food items during the year, preceding enrollment. Further information was sought on consumption frequency for different subitems, preparation methods, and additions. Color photographs were used to estimate portion size for 28 food items. Overall, the questionnaire allows the estimation of the average daily consumption of 178 foods, by asking for subitems for several food items, like fruit and vegetables, in additional questions. The FFQ had been validated in pilot studies before start of the study (20,21) against 12 24-h recalls. Spearman correlations were 0.76 for carbohydrates and 0.74 for fiber, and 0.78, 0.56, 0.69, and 0.70 for bread, fruit, sweets, and potatoes, respectively. Therefore, the FFQ seems reasonably valid for ranking individuals according to food group intake, particularly those that contribute most to glycemic load. The glycemic index of the foods was obtained from the international table compiled by Foster-Powell et al. (22). This table brought together all relevant data published between 1981 and 2001. For foods with ≥2 published values, mean (±SEM) glycemic index was calculated and listed in the table.

Calculation of dietary glycemic load. We calculated glycemic load by multiplying the glycemic index of a food with its carbohydrate content, then multiplied this value with the frequency of consumption of this food and summed the values over all food items (12). Glycemic load thus represents both quality and quantity of carbohydrates and interaction between the two. Each unit of dietary glycemic load represents the equivalent of 1-g carbohydrate from glucose. The overall glycemic index of a woman's diet was calculated by dividing the dietary glycemic load by the total amount of carbohydrate consumed (12). Such expression of dietary glycemic index per gram of carbohydrate thus reflects the overall quality of the daily carbohydrate intake. As expected from its calculation, dietary glycemic load correlated well with carbohydrate intake ($r = 0.93$), but this was not the case for dietary glycemic index ($r = 0.18$).

Morbidity and mortality follow-up. Data on morbidity were obtained from the Dutch Centre for Health Care Information, which holds a standardized computerized register of hospital discharge diagnoses. Admission files have been filed continuously from all general and university hospitals in the Netherlands from 1990. Data on gender, date of birth, and dates of admission and discharge were recorded whenever a patient is discharged from hospital. One mandatory principal diagnosis and up to 9 optional additional diagnoses were reported. All diagnoses were coded according to the ICD-9-CM. Coding of the diagnoses is performed by qualified medical administrative personnel in the hospitals. The National Medical Registry collects these data in the Hospital Discharge Diagnosis Database. These data are checked by the National Medical Registry, mistakes are corrected by the hospitals, and unlikely diagnoses are discussed with the hospital. Follow-up was complete until January 1, 2005. The database was linked to the cohort on the basis of birth date, gender, postal code, and general practitioner with a validated probabilistic method (23).

Information on vital status was obtained through linkage with the municipal administration registries. Causes of death were obtained from the women's general practitioners and coded by 2 independent physicians (P.H.M.P., M.L.B.). Discordant coding was solved in consensus. For our analysis, CHD (ICD-9-CM 410 to 414, 427.5) and cerebrovascular events (CVA) (ICD-9-CM 430 to 438), whichever came first, were the end points of interest.

Data analyses. Baseline characteristics in quartiles of energy-adjusted dietary glycemic load were inspected using analysis of variance for continuous variables and a chi-square test for categorical variables. We calculated person-years of follow-up for each participant from the date of return of the questionnaire to the date of CHD or CVA diagnosis, the date of death, or January 1, 2005. Mortality due to noncardiovascular causes ($n = 549$), loss to follow-up due to emigration ($n = 60$) and withdrawn alive ($n = 14,306$) were considered censoring events. We used Cox regression to estimate hazard ratios (HRs) for CVD, CHD, and CVA within quartiles of glycemic load and glycemic index using the lowest quartile as reference. Linear trends across quartiles of glycemic load and glycemic index were determined by including quartiles in the model as a linear covariate. We adjusted for established cardiovascular risk factors or nutritional factors using a stepwise approach. First we included age, smoking, pack-years, hypertension, hypercholesterolemia, BMI, mean systolic blood pressure, total physical activity, menopausal status, and HRT and OC use into the Cox model with glycemic load to see whether the crude HR of glycemic load changed substantially. Body mass index was entered as a categorical variable (≤20, 20.1 to 25, 26 to 30, >30 kg/m^2). Nutritional variables were included next (intake of total energy, vitamin E, multivitamins, alcohol, protein, fiber, and folate), except fat intake. Alcohol was entered as a categorical variable (≤10, 11 to 25, 26 to 50, >50 g/day), with the second lowest category (11 g alcohol/day to 25 g alcohol/day) as the reference group, as this best describes the U-shaped relationship between alcohol-intake and CVD risk. Finally, we included intake of saturated, mono-, and polyunsaturated fat. To control for total energy intake, all nutrients and glycemic load were adjusted for total energy intake using the residual method (12). In sensitivity analyses, HRs were also adjusted for waist-hip ratio (instead of BMI). We investigated the interaction of glycemic index and glycemic load with predetermined subgroups of BMI (≤25 vs. >25 kg/m^2) by including interaction terms of glycemic index and glycemic load with BMI in the model. Associations of glycemic load and glycemic index with biomarkers were determined by linear regression using the previously described, multivariate models (model 4).

Analyses were performed using SPSS version 14.0 (SPSS Inc., Chicago, Illinois).

Results

Table 1 shows baseline characteristics in quartiles of energy-adjusted dietary glycemic load. Mean energy-adjusted dietary glycemic load varied <2-fold between the highest and lowest quartile of energy-adjusted dietary glycemic load of the study population, with an average dietary glycemic load of 100 (±17) in the population. Women with high dietary glycemic loads consumed more carbohydrates and dietary fiber but less protein, alcohol, and fats. Women with high dietary glycemic loads had lower BMI, waist-hip ratio, lower prevalence of smoking, and used fewer hormones than women with low dietary glycemic loads. Table 2 shows the contribution of particular foods to the dietary glycemic load. Potatoes, bread, fruit, and sweets contributed most to glycemic load.

We documented 556 incident cases of fatal or nonfatal CHD and 243 incident cases of fatal or nonfatal CVA during 141,633 person-years of follow-up. Adjusting for classical CVD risk factors (model 2, Table 3), the estimated HR between the highest and lowest quartile of glycemic load was 1.20 (95% confidence interval [CI] 0.98 to 1.47; $p_{trend} = 0.08$). Including nutrition variables except fat intake did not materially change the HR (model 3, Table 3). Including fat intake in the model augmented the association with an HR for the highest compared with lowest quartile of glycemic load of 1.47 (95% CI 1.04 to 2.09; p_{trend} =

Table 1 Baseline Characteristics* According to Quartiles of Energy-Adjusted Glycemic Load Among 15,714 Women

Variable	Quartile of Energy-Adjusted Dietary Glycemic Load				p Value for Difference Across Quartiles
	1	2	3	4	
n	3,911	3,920	3,937	3,946	
Quartile mean score of glycemic load	78.5 ± 9.1	95.2 ± 3.2	105.9 ± 3.2	121.8 ± 8.8	
Age (yrs)	56 ± 6	57 ± 6	57 ± 6	58 ± 6	<0.001
Person months of follow-up (months)	108 ± 21	108 ± 22	108 ± 21	108 ± 22	0.87
Systolic blood pressure (mm Hg)	132 ± 20	132 ± 20	133 ± 20	133 ± 20	0.051
Diastolic blood pressure (mm Hg)	80 ± 10	79 ± 10	79 ± 10	79 ± 10	<0.001
Body mass index (kg/m^2)	26.0 ± 4.0	26.2 ± 4.1	25.9 ± 4.0	25.5 ± 3.9	<0.001
Physical activity	6.7 ± 5.0	7.0 ± 5.0	7.1 ± 5.0	6.9 ± 5.1	0.002
Waist-hip ratio	0.79 ± 0.06	0.79 ± 0.06	0.79 ± 0.06	0.78 ± 0.06	<0.001
Smoking (%)					<0.001
Never	28.5	42.2	49.5	54.0	
Past	37.7	36.6	33.8	29.8	
Current ≤10/day	13.0	10.2	8.9	8.8	
Current 11–20/day	14.0	8.0	5.7	5.7	
Current >20/day	6.8	2.9	2.2	1.7	
Hypertension (%)	17.8	18.5	18.5	18.6	0.78
Hypercholesterolemia (%)	3.6	3.3	5.2	6.3	<0.001
Menopausal status (%)					<0.001
Premenopausal	11.9	11.3	9.3	9.5	
Postmenopausal	70.4	73.9	76.7	78.3	
Unknown	17.7	14.8	14.0	12.2	
HRT use (%)	29.1	25.9	25.1	23.6	<0.001
OC use (%)	70.7	65.4	64.1	59.1	<0.001
Nutrients†					
Total energy (kJ)	7,512 ± 1,883	7,643 ± 1,821	7,604 ± 1,779	7,477 ± 1,802	<0.001
Carbohydrates (g)	162.1 ± 17.1	187.5 ± 11.1	203.6 ± 10.9	227.2 ± 16.2	<0.001
Protein (g)	72.1 ± 10.8	71.8 ± 9.7	70.2 ± 9.0	65.9 ± 9.3	<0.001
Total fat	74.5 ± 11.5	71.6 ± 8.8	67.8 ± 7.5	61.3 ± 8.0	<0.001
Polyunsaturated fat (g)	13.8 ± 3.9	13.4 ± 3.4	12.9 ± 3.2	12.0 ± 3.3	<0.001
Monounsaturated fat (g)	28.3 ± 5.0	26.6 ± 3.9	24.9 ± 3.4	22.1 ± 3.5	<0.001
Saturated fat (g)	31.4 ± 6.1	30.6 ± 5.0	29.1 ± 4.3	26.3 ± 4.3	<0.001
Cholesterol (mg)	231.5 ± 81.4	218.5 ± 69.7	200.8 ± 66.0	170.8 ± 60.5	<0.001
Dietary fiber (g)	20.0 ± 3.8	21.9 ± 3.8	23.0 ± 4.0	24.0 ± 4.7	<0.001
Dietary fiber per 200 kcal carbohydrates (g)	6.2 ± 1.2	5.9 ± 1.1	5.7 ± 1.0	5.3 ± 1.1	<0.001
Alcohol (g)	20.0 ± 18.5	8.7 ± 10.0	5.5 ± 7.3	2.8 ± 4.6	<0.001
Dietary vitamin E (mg)	10.9 ± 3.2	11.1 ± 2.8	10.9 ± 2.8	10.6 ± 2.8	<0.001
Folate (μg)	193.0 ± 42.3	195.9 ± 38.9	196.0 ± 39.0	193.3 ± 38.6	<0.001

*Mean ± SD, unless stated otherwise; †all dietary variables were adjusted for total energy intake, except energy and cholesterol intake.
HRT = hormone replacement therapy; OC = oral contraceptives.

Table 2 Mean Daily Intake of Individual Foods According to Quartiles of Energy-Adjusted Dietary Glycemic Load

	Quartile of Energy-Adjusted Dietary Glycemic Load			
Foods (g/day)*	1	2	3	4
Drinks	1,625	1,537	1,525	1,519
Bread	93	108	119	131
Potatoes	76	82	85	86
Eggs	17	16	15	12
Fruit	186	224	246	268
Cake	22	31	35	39
Wheat products	29	33	35	39
Vegetables	143	138	135	128
Cheese	42	37	34	28
Milk products	380	425	427	394
Nuts and snacks	14	12	10	8
Legumes	9	9	9	9
Soups	71	67	64	58
Sweets	15	22	28	40
Fats	37	36	35	32
Fish	12	11	10	9
Meat	105	91	82	67

*All foods were adjusted for total energy intake.

0.03). Dietary glycemic index showed a similar positive association with CVD with an HR adjusted for classical risk factors of 1.42 (95% CI 1.17 to 1.73) for the highest versus lowest quartile (p_{trend} = 0.001). Adjusting for nutrients and fat intake slightly attenuated the HR for CVD to 1.33 (95% CI 1.07 to 1.67) for the highest versus lowest quartile (p_{trend} = 0.02).

In separate analyses for CHD and CVA end points adjusting for all covariates in the full model (M4), we observed similar associations of glycemic load with CHD ($HR_{Q4\ vs.\ Q1}$ 1.44; 95% CI 0.95 to 2.19; p_{trend} = 0.14) and CVA ($HR_{Q4\ vs.\ Q1}$ 1.55; 95% CI 0.81 to 2.97; p_{trend} = 0.10). Glycemic index, however, was more strongly associated with CHD ($HR_{Q4\ vs.\ Q1}$ 1.44; 95% CI 1.10 to 1.89; p_{trend} = 0.01) than CVA end points ($HR_{Q4\ vs.\ Q1}$ 1.12; 95% CI 0.75 to 1.69; p_{trend} = 0.61). We adjusted for waist/hip ratio instead of BMI, but this did not affect our results for glycemic load ($HR_{Q4\ vs.\ Q1}$ 1.47; 95% CI 1.04 to 2.09; p_{trend} = 0.03) or glycemic index ($HR_{Q4\ vs.\ Q1}$ 1.32; 95% CI 1.05 to 1.65; p_{trend} = 0.03). Similarly, adjusting for total energy-adjusted fat intake instead of different fatty acids did not affect associations of glycemic load ($HR_{Q4\ vs.\ Q1}$ 1.46; 95% CI 1.03 to 2.08; p_{trend} = 0.04) and glycemic index ($HR_{Q4\ vs.\ Q1}$ 1.35; 95% CI 1.08 to 1.68; p_{trend} = 0.02).

We also investigated the association of total carbohydrates, mono- and disaccharides, and polysaccharides with CVD risk, but no significant associations were observed (Table 4). In separate analyses for lean and overweight women adjusted according to the full model M4, we observed that BMI may modify the association between glycemic load and CVD and to a lesser extent for glycemic index (Table 5). The association between glycemic load and CVD risk was virtually absent in normal weight women ($HR_{Q4\ vs.\ Q1}$ 1.14; 95% CI 0.67 to 1.93; p_{trend} = 0.43) and most pronounced for overweight women ($HR_{Q4\ vs.\ Q1}$ 1.78; 95% CI 1.11 to 2.85; p_{trend} = 0.04); the p value for interaction was 0.19. Body mass index did not modify the association of glycemic index with CVD risk.

Finally, we assessed associations of dietary glycemic load and glycemic index with several biomarkers. In fully adjusted models (model 4), HDL cholesterol was inversely associated with glycemic load (β: −0.005 ± 0.001; p <

Table 3 Adjusted Hazard Ratios (With 95% CI) of Cardiovascular Disease According to Quartiles of Energy-Adjusted Dietary Glycemic Load and Glycemic Index Among 15,714 Women

	Quartile of Energy-Adjusted Glycemic Load				
	1*	2	3	4	p Value for Trend
Cases	189	193	198	219	
Crude	1.00	1.02 (0.83–1.24)	1.04 (0.85–1.27)	1.14 (0.94–1.39)	0.175
M1: age	1.00	0.94 (0.77–1.15)	0.93 (0.76–1.13)	0.99 (0.81–1.20)	0.91
M2: multivariate†	1.00	1.08 (0.89–1.33)	1.10 (0.90–1.35)	1.20 (0.98–1.47)	0.082
M3: M2 + nutrients‡	1.00	1.01 (0.82–1.26)	1.02 (0.80–1.28)	1.12 (0.86–1.45)	0.40
M4: M3 + all fat§	1.00	1.13 (0.89–1.42)	1.21 (0.92–1.60)	1.47 (1.04–2.09)	0.033
	Quartile of Energy-Adjusted Glycemic Index				
	1*	2	3	4	p Value for Trend
Cases	180	201	190	228	
Crude	1.00	1.12 (0.91–1.37)	1.06 (0.86–1.30)	1.28 (1.05–1.55)	0.029
M1: age	1.00	1.07 (0.88–1.31)	1.06 (0.86–1.30)	1.42 (1.17–1.73)	0.001
M2: multivariate†	1.00	1.15 (0.94–1.40)	1.13 (0.92–1.39)	1.42 (1.16–1.73)	0.001
M3: M2 + nutrients‡	1.00	1.11 (0.90–1.37)	1.09 (0.88–1.35)	1.36 (1.09–1.69)	0.012
M4: M3 + all fat§	1.00	1.11 (0.90–1.36)	1.08 (0.87–1.35)	1.33 (1.07–1.67)	0.020

*Reference category. †Adjusted for age; hypertension; cholesterolemia; smoking (never/past/current smoking of 1 to 10, 11 to 20, and >20 cigarettes); body mass index (≤20, 20.1 to 25, 26 to 30, >30 kg/m^2); mean systolic blood pressure; total physical activity; menopausal status (pre or post); hormone replacement therapy use; and oral contraceptives use. ‡Adjusted for alcohol intake (≤10, 11 to 25, 26 to 50, >50 g/day energy-adjusted), total energy intake (in quintiles), and energy-adjusted intake of vitamin E; protein; dietary fiber; and folate and covariates from footnote *. §Adjusted for energy-adjusted intake of saturated fat, poly- and monounsaturated fat, and covariates from footnotes † and ‡.

CI = confidence interval; M = model.

Table 4 Adjusted* Hazard Ratios (With 95% Confidence Intervals) of Cardiovascular Disease According to Quartiles of Energy-Adjusted Carbohydrates, Mono- and Disaccharides, and Polysaccharides Among 15,714 Women

	Quartile of Energy-Adjusted Carbohydrate Intake				p Value for Trend
	1†	2	3	4	
Carbohydrates	1.00	1.02 (0.80–1.30)	1.14 (0.84–1.54)	1.17 (0.78–1.77)	0.35
Mono- and disaccharides‡	1.00	0.91 (0.73–1.15)	1.00 (0.77–1.31)	1.04 (0.72–1.48)	0.70
Polysaccharides‡	1.00	1.13 (0.92–1.39)	1.02 (0.81–1.29)	0.99 (0.75–1.32)	0.78

*Adjusted for age; hypertension; cholesterolemia; smoking (never/past/current smoking of 1 to 10, 11 to 20, and >20 cigarettes); body mass index; mean systolic blood pressure; total physical activity; menopausal status (pre or post); hormone replacement therapy use; oral contraceptives use; alcohol intake (≤10, 11 to 25, 26 to 50, >50 g/day energy-adjusted); total energy intake (in quintiles) and energy-adjusted intake of vitamin E; protein; dietary fiber; folate; saturated fat; and poly- and monounsaturated fat. †Reference category. ‡Mono-, di-, and polysaccharides were included simultaneously.

0.001), and LDL cholesterol tended to be associated with glycemic load (β: 0.005 ± 0.003; p = 0.12). Glycemic index was also inversely associated with HDL cholesterol concentrations (β: −0.83 ± 0.30; p = 0.006). No significant associations with total cholesterol, glucose, or CRP concentrations were observed.

Discussion

In this population of Dutch women consuming a modest glycemic load diet, high dietary glycemic load and glycemic index increased risk of CVD independent of known cardiovascular risk factors and dietary variables. For glycemic load, this association was similar for CHD and CVA, but for glycemic index, the association was more pronounced for CHD. Glycemic load was particularly associated with CVD among overweight women.

Few studies have investigated the association of dietary glycemic load and glycemic index with CVD. This is the first study to report increased risks in a population consuming modest glycemic load diet. A previous study among U.S. women reported an approximately doubled risk of CHD in the highest glycemic load quintile (12). Overall dietary glycemic index was also associated with increased risk of CHD. A more recent report from this study confirmed these relations (13). For CVA, however, a more recent study of Oh et al. (15) reported a positive association between glycemic load and total stroke among overweight women, while no such relation was observed for glycemic index. Our results are consistent with those studies, also when differentiated for CHD and CVA events. In these studies, however, the mean energy-adjusted dietary glycemic load ranged from approximately 100 in the lowest to 200 in the highest quintile, while in our study glycemic load ranged from 79 in the lowest to 122 in the highest quartile. This could be due to the use of white bread as the reference for the glycemic index as opposed to glucose in our study. However, when applying a correction factor of 0.7 to the glycemic indexes based on white bread, the figures still suggest lower glycemic loads of the diets in the Netherlands than U.S. Even in these lower ranges, both dietary glycemic load and glycemic index were associated with CVD risk, although less pronounced than among U.S. women. Of note, van Dam et al. (14) did not find an association between glycemic index and cardiovascular risk among 646 men from the Zutphen Elderly study. Similarly, an Italian case-control study from Tavani et al. (24) consisting of 433 nondiabetic subjects with a first episode of nonfatal acute myocardial infarction and 488 control subjects could not

Table 5 Adjusted* HRs Among BMI Subgroups According to Quartiles of Dietary Glycemic Load and Glycemic Index

	Quartiles	Adjusted HR (95% CI) for BMI, Low (≤25 kg/m^2)	Adjusted HR (95% CI) for BMI, High (>25 kg/m^2)	p Value for Interaction
Glycemic load				
	1†	1.0†	1.0†	
	2	0.96 (0.66–1.39)	1.28 (0.94–1.74)	
	3	1.17 (0.78–1.78)	1.25 (0.86–1.82)	
	4	1.14 (0.67–1.93)	1.78 (1.11–2.85)	
	p value for trend	0.43	0.04	0.19
Glycemic index				
	1†	1.0†	1.0†	
	2	1.24 (0.91–1.71)	1.02 (0.77–1.35)	
	3	1.01 (0.72–1.42)	1.15 (0.87–1.53)	
	4	1.36 (0.97–1.92)	1.31 (0.97–1.76)	
	p value for trend	0.19	0.06	0.13

*Adjusted for: age; hypertension; cholesterolemia; smoking (never/past/current smoking of 1 to 10, 11 to 20, and >20 cigarettes); body mass index (BMI); mean systolic blood pressure; total physical activity; menopausal status (pre or post); hormone replacement therapy use; oral contraceptives use; alcohol intake (≤10, 11 to 25, 26 to 50, >50 g/day energy-adjusted); total energy intake (in quintiles); and energy-adjusted quintiles of vitamin E, protein, dietary fiber, folate, saturated fat, and poly- and monounsaturated fat. †Reference category.
CI = confidence interval; HR = hazard ratio.

disclose an increased risk of CVD with high dietary glycemic load. However, relative risks were not adjusted for fat intake, which may have attenuated their results. They did not observe a significant association of glycemic index with CVD risk as well, but the odds ratio of 1.38 (95% CI 0.95 to 2.00; $p_{trend} = 0.10$) is comparable to our results.

Like our study, Tavani et al. (24) did find a significant association for glycemic index among overweight people. Liu et al. (12) also observed that the increased risk of CHD with high dietary glycemic load was most pronounced among women with BMIs >23 kg/m^2, but absent among women with a BMI <23 kg/m^2. Oh et al. (15) reported a positive association of glycemic load with total stroke only among overweight women (BMI ≥25 kg/m^2). Although interactions did not reach significance, results from our study are consistent.

The mechanism by which glycemic load increases risk of CVD is not completely elucidated, but effects on insulin resistance and blood lipid profile are thought to be involved. Carbohydrates with high glycemic loads produce substantial postprandial blood glucose and insulin responses. The rapid blood glucose decline due to insulin secretion within a few hours after consumption creates a state of hunger (25), leading to continued intake of high-glycemic load meals and aggravated postprandial glycemia. Over time, these postprandial responses may contribute to insulin resistance and obesity (26,27). In turn, insulin resistance and obesity increase triglycerides and LDL cholesterol concentrations and decrease HDL concentrations, all components of the metabolic syndrome. Indeed, several intervention studies show decreased triglyceride and LDL cholesterol concentrations after a low glycemic index diet (28). Recently, a study by McMillan-Price et al. (29) compared reduced-fat diets with high protein or carbohydrate contents with differing glycemic index. Their results showed that both high-protein and high-carbohydrate diets increased body fat loss, but a low glycemic index diet also optimized blood lipid profile. Results from our study confirm these relations with blood lipid profile.

A strength of this study is its prospective design, particularly eliminating recall bias. As in any observational study, our results could be influenced, at least in part, by differences in factors other than glycemic load. It has been suggested that high dietary glycemic load is the result of a high intake of fiber-depleted foods (28), and, therefore, high glycemic load may be a marker for an unhealthy lifestyle. However, we simultaneously adjusted for smoking, alcohol, physical activity, and fiber intake in our analysis, and still observed an increased CHD risk for higher glycemic loads. We additionally adjusted for educational status as a proxy for such health-conscious behaviors with similar results (data not shown). In addition, this study population was homogeneous with respect to gender and age, reducing residual confounding, but limiting our ability to generalize to men. Nevertheless, we cannot exclude residual confounding by unknown risk factors.

A particular concern in such observational study is misclassification of dietary exposure. We used an FFQ to quantify the average exposure to dietary glycemic load and glycemic index in the previous year, but it was not specifically designed to estimate dietary glycemic load. However, a validation study showed good agreement of the FFQ with 24-h recalls for carbohydrate and fiber intake, and specific food groups contributing most to dietary glycemic load (20,21). It is, therefore, unlikely that the calculated dietary glycemic load contains large errors. Another concern regarding data of dietary glycemic index is that it could simply reflect carbohydrate intake. However, we have shown that the correlation of dietary glycemic index with carbohydrate intake is poor. In addition, carbohydrate intake itself was not associated with CVD. Therefore, our results specifically reflect the carbohydrate quality of the diet and not the carbohydrate intake itself.

Finally, the concept of glycemic load and glycemic index is criticized for limited applicability in daily practice, also given recent results from large-scale diet interventions (30). However, the concept is currently implemented in nutrition guidelines in Australia through labeling of foods with a symbol and their glycemic index value (31), suggesting that it is applicable in public health recommendations.

In conclusion, our findings show that high dietary glycemic load and glycemic index increase the risk of CVD, also in a population consuming a modest glycemic load diet. For glycemic load, this association was similar for CHD and CVA, while glycemic index seems particularly associated with CHD. These harmful effects may particularly affect overweight women.

Acknowledgments

The authors are grateful for the skillful help of J.J.M.M. Drijvers, dietician, and J.H. den Breeijen, data manager, in calculating glycemic load.

Reprint requests and correspondence: Dr. Joline W. J. Beulens, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Room STR 6.131, P.O. Box 85500, 3508 GA Utrecht, the Netherlands. E-mail: J.Beulens@umcutrecht.nl.

REFERENCES

1. Liu S, Manson JE, Stampfer MJ, et al. Dietary glycemic load assessed by food-frequency questionnaire in relation to plasma high-density-lipoprotein cholesterol and fasting plasma triacylglycerols in postmenopausal women. Am J Clin Nutr 2001;73:560–6.
2. Jeppesen J, Schaaf P, Jones C, Zhou MY, Chen YD, Reaven GM. Effects of low-fat, high-carbohydrate diets on risk factors for ischemic heart disease in postmenopausal women. Am J Clin Nutr 1997;65:1027–33.
3. Ludwig DS. Glycemic load comes of age. J Nutr 2003;133:2695–6.
4. Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34:362–6.
5. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA 1997;277:472–7.

6. Grundy SM, Brewer HB Jr., Cleeman JI, Smith SC Jr., Lenfant C. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. Circulation 2004;109:433–8.
7. Stein E. The lower the better? Reviewing the evidence for more aggressive cholesterol reduction and goal attainment. Atheroscler Suppl 2002;2:19–23.
8. Nanchahal K, Morris JN, Sullivan LM, Wilson PW. Coronary heart disease risk in men and the epidemic of overweight and obesity. Int J Obes (Lond) 2005;29:317–23.
9. Hu FB, Stampfer MJ, Solomon CG, et al. The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. Arch Intern Med 2001;161:1717–23.
10. Salmeron J, Ascherio A, Rimm EB, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care 1997;20:545–50.
11. Brand-Miller JC. Glycemic load and chronic disease. Nutr Rev 2003;61:S49–55.
12. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr 2000;71:1455–61.
13. Halton TL, Willett WC, Liu S, et al. Low-carbohydrate-diet score and the risk of coronary heart disease in women. N Engl J Med 2006;355:1991–2002.
14. van Dam RM, Visscher AW, Feskens EJ, Verhoef P, Kromhout D. Dietary glycemic index in relation to metabolic risk factors and incidence of coronary heart disease: the Zutphen Elderly study. Eur J Clin Nutr 2000;54:726–31.
15. Oh K, Hu FB, Cho E, et al. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. Am J Epidemiol 2005;161:161–9.
16. Riboli E. Nutrition and cancer: background and rationale of the European Prospective Investigation into Cancer and Nutrition (EPIC). Ann Oncol 1992;3:783–91.
17. Boker LK, van Noord PA, van der Schouw YT, et al. Prospect-EPIC Utrecht: study design and characteristics of the cohort population. European Prospective Investigation into Cancer and Nutrition. Eur J Epidemiol 2001;17:1047–53.
18. Voorrips LE, Ravelli AC, Dongelmans PC, Deurenberg P, Van Staveren WA. A physical activity questionnaire for the elderly. Med Sci Sports Exerc 1991;23:974–9.
19. Little RA, Rubin DB. Statistical Analysis With Missing Data. New York, NY: Wiley, 1987.
20. Ocke MC, Bueno-de-Mesquita HB, Goddijn HE, et al. The Dutch EPIC food frequency questionnaire. I. Description of the questionnaire, and relative validity and reproducibility for food groups. Int J Epidemiol 1997;26 Suppl 1:S37–48.
21. Ocke MC, Bueno-de-Mesquita HB, Pols MA, Smit HA, Van Staveren WA, Kromhout D. The Dutch EPIC food frequency questionnaire. II. Relative validity and reproducibility for nutrients. Int J Epidemiol 1997;26 Suppl 1:S49–58.
22. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr 2002;76:5–56.
23. Herings RM, Bakker A, Stricker BH, Nap G. Pharmaco-morbidity linkage: a feasibility study comparing morbidity in two pharmacy based exposure cohorts. J Epidemiol Community Health 1992;46:136–40.
24. Tavani A, Bosetti C, Negri E, Augustin LS, Jenkins DJ, La VC. Carbohydrates, dietary glycaemic load and glycaemic index, and risk of acute myocardial infarction. Heart 2003;89:722–6.
25. Bell SJ, Sears B. Low-glycemic-load diets: impact on obesity and chronic diseases. Crit Rev Food Sci Nutr 2003;43:357–77.
26. Pi-Sunyer FX. Glycemic index and disease. Am J Clin Nutr 2002;76:290S–8S.
27. Saris WH. Sugars, energy metabolism, and body weight control. Am J Clin Nutr 2003;78:850S–7S.
28. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA 2002;287:2414–23.
29. Millan-Price J, Petocz P, Atkinson F, et al. Comparison of 4 diets of varying glycemic load on weight loss and cardiovascular risk reduction in overweight and obese young adults: a randomized controlled trial. Arch Intern Med 2006;166:1466–75.
30. Howard BV, Van HL, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. JAMA 2006;295:655–66.
31. The Glycemic Index (GI) Symbol Program. Available at: http://www.gisymbol.com.au. Accessed January 31, 2007.